

**PCT**  
**NOTIFICATION OF ELECTION**  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)  
10 December 1999 (10.12.99)

International application No.  
PCT/GB99/01211

Applicant's or agent's file reference  
P21483/RMC

International filing date (day/month/year)  
21 April 1999 (21.04.99)

Priority date (day/month/year)  
22 April 1998 (22.04.98)

Applicant

NELSON, John et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
22 November 1999 (22.11.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

REPLACED BY  
ART 34 AMDT

WO 99/54356

PCT/GB99/01211

28

1 CLAIMS

2

3 1 Use of a peptide factor derived from amino acid  
4 residues 33 to 42 of murine epidermal growth or a  
5 synthetic equivalent thereof in the preparation of a  
6 medicament to target laminin receptors.

7

8 2 A peptide factor derived from amino acid residues 33  
9 to 42 of murine epidermal growth factor peptide or a  
10 synthetic equivalent thereof wherein the peptide  
11 factor is modified to protect it from proteolytic  
12 degradation and the peptide binds to laminin  
13 receptors.

14

15 3 A peptide factor as claimed in claim 2 wherein the  
16 modifications consist of at least one modification  
17 chosen from the group comprising; substitution of  
18 tyrosine by tyrosine analogues, substitution of  
19 arginine by arginine analogues, capping the N  
20 terminal of the peptide capping the C terminal of the  
21 peptide and capping thiol groups of cysteines.

22

23 4 A peptide as claimed in claim 2 or claim 3 wherein  
24 the peptide has the sequence.

25

26 Acetyl-C-[S-Acm]-VIGYSGDR-C-[S-Acm]NH<sub>2</sub>

27

28 5 A peptide as claimed in claim 3 wherein tyrosine is  
29 substituted by Tic-OH.

30

31 6 A peptide as claimed in claim 3 wherein arginine is  
32 substituted by Citrulline.

33

34 7 Use of a peptide factor as claimed in claim 1 in the  
35 preparation of a medicament to bind laminin receptors

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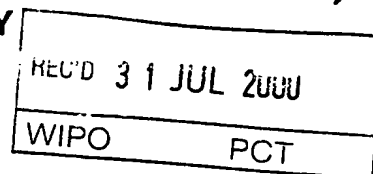
- 1 as an antagonist.  
2  
3 8 Use of a peptide factor as claimed in claim 1 in the  
4 preparation of a medicament to bind laminin receptors  
5 as an agonist.  
6  
7 9 Use as claimed in claim 8 in the preparation of a  
8 medicament for healing endothelial cell wounding.  
9  
10 10 Use as claimed in claim 8 or 9 for the treatment of  
11 retinopathy of immaturity.  
12

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



16

Applicant's or agent's file reference P21483/RMC		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/01211	International filing date (day/month/year) 21/04/1999	Priority date (day/month/year) 22/04/1998	
International Patent Classification (IPC) or national classification and IPC C07K14/485			
Applicant THE QUEEN'S UNIVERSITY OF BELFAST et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  22/11/1999	Date of completion of this report  24.07.00
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Stolz, B  Telephone No. +49 89 2399 8416  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01211

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

**Description, pages:**

1-27 as originally filed

**Claims, No.:**

1-8 as received on 16/06/2000 with letter of 16/06/2000

**Drawings, sheets:**

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01211

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	3, 4, 6-8
	No:	Claims	1, 2, 5
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/01211

1. Reasoned statement

1.1. The present application describes peptide factors derived from mEGF<sub>33-42</sub>, and the use of certain peptide factors in medical treatment.

1.2. Novelty (Art. 33(2) PCT)

The subject matter of claims 1 to 8 is novel as none of the cited items of prior art describes mEGF<sub>33-42</sub> derived peptides having either Tyr or Arg analogs.

1.3. Inventive step (Art. 33(3) PCT)

The closest prior art, Nelson et al., 1996, describes binding of mEGF<sub>33-42</sub> as a laminin antagonist to the 67kD laminin receptor. The peptide is said to have antimetastatic potential and the position of Y5 and R9 are said to be important for receptor binding. In light of this document, the technical problem underlying the present application is identified as the provision of mEGF<sub>33-42</sub> analogs. The solution to this problem are analogs protected from proteolytic degradation and having at least Y5 substituted by tyrosine analogs and/or R9 substituted by arginine analogs.

The gist of the application concerns modification of the Y5 and R9 sidechains which results in unexpected effects, i.e. the respective analogs show improved binding properties or in case of substituting TicOH for Y even a reversal from antagonist to agonist (cf. e.g. p. 25 of the description). Thus, claims 3 and 4 are considered to involve an inventive step.

However, claims 1 and 2 comprise not only modifications of the side chains at positions 5 and 9 but also modifications of the peptide bonds (cf. p. 6, paragraph 3, of the description). Modifying the peptide bonds in order to render the analogs protease resistant is considered to be within easy reach of the person of skill, not requiring inventive step. The selection of positions 5 and 9 for such modifications is, in the absence of a demonstrated unexpected effect, considered to be arbitrary and hence not involving an inventive step. Likewise, modification of the N- and C-terminus does not add the required inventive element. Such compounds would

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/01211

also find use as laminin antagonists. Therefore, claims 1, 2 and 5 lack inventive step.

2. Certain observations

- 2.1. A characterizing feature of claim 1 is "protection from proteolytic degradation". Yet, the application does not provide any information on how this parameter is assessed. There may be several procedures in the art leading to different results. As a consequence, the person of skill cannot be sure about the meaning of the term and ultimately the scope of the claim.



16-06-2000

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1 CLAIMS

2

3 1 A peptide factor derived from amino acid residues 33  
4 to 42 of murine epidermal growth factor peptide or a  
5 synthetic equivalent thereof wherein the peptide  
6 factor is modified to protect it from proteolytic  
7 degradation and the peptide binds to laminin  
8 receptors wherein the modifications consist of at  
9 least one modification chosen from the group  
10 comprising; substitution of tyrosine by tyrosine  
11 analogues and substitution of arginine by arginine  
12 analogues,

13

14 2 A peptide as claimed in Claim 1 wherein the  
15 peptide is further modified by at least one  
16 modification chosen from the group comprising  
17 capping the N terminal of the peptide, capping  
18 the C terminal of the peptide and capping thiol  
19 groups of cysteines.

20

21 3 A peptide as claimed in claims 1 or 2 wherein  
22 tyrosine is substituted by Tic-OH.

23

24 4 A peptide as claimed in claims 1, 2 or 3 wherein  
25 arginine is substituted by Citrulline.

26

27 5 Use of a peptide factor as claimed in any of the  
28 preceding claims in the preparation of a medicament  
29 to bind laminin receptors as an antagonist.

30

31 6 Use of a peptide factor as claimed in any of the  
32 preceding claims in the preparation of a medicament  
33 to bind laminin receptors as an agonist.

34

35 7 Use as claimed in claim 6 in the preparation of a  
36 medicament for healing endothelial cell wounding.

16-06-2000

GB 009901211

2

- 1 8 Use as claimed in claim 8 or 9 for the treatment of
- 2 retinopathy of immaturity.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P21483/RMC</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/GB 99/ 01211</b>	International filing date (day/month/year) <b>21/04/1999</b>	(Earliest) Priority Date (day/month/year) <b>22/04/1998</b>
Applicant  <b>THE QUEEN'S UNIVERSITY OF BELFAST et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PEPTIDE FRAGMENTS OF MURINE EPIDERMAL GROWTH FACTOR AS LAMININ RECEPTOR TARGETS**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/01211

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07K14/485 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 686 283 A (NESTOR JR JOHN J ET AL) 11 August 1987 (1987-08-11) claims; examples ---	1-3,7-10
X	BAILIE, J. R. ET AL: "Synthesis and receptor-binding activity of peptide fragments of epidermal growth factor" BIOCHEM. SOC. TRANS. (1989), 17(2), 409-10 ,1989, XP002116635 page 409, right-hand column; table 1 ---	1-4,7-10
X	MCFERRAN, NEIL V. ET AL: "A peptide molecular dynamics study correlates structure with function" BIOCHEM. SOC. TRANS. (1996), 24(1), 127S , 1996, XP002116636 page 127S, left-hand column, paragraph 4 ---	1-4,7-10
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
"&" document member of the same patent family

Date of the actual completion of the international search

27 September 1999

Date of mailing of the international search report

12/10/1999

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Fuhr, C

1

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01211

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NELSON, JOHN ET AL: "Murine epidermal growth factor (EGF) fragment (33-42) inhibits both EGF- and laminin-dependent endothelial cell motility and angiogenesis" CANCER RES. (1995), 55(17), 3772-6 ,1995, XP002116637 page 228 -----	1-3,7-10
X	NELSON, JOHN ET AL: "Murine epidermal growth factor peptide (33-42) binds to a YIGSR-specific laminin receptor on both tumor and endothelial cells" J. BIOL. CHEM. (1996), 271(42), 26179-26186 ,1996, XP002116638 page 26183, left-hand column, paragraph 3 -page 26186, left-hand column, last paragraph -----	1

### Information on patent family members

CT/GB 99/01211

Patent document  
cited in search report

Publication  
date

Patent family member(s)

Publication  
date

US 4686283

A

11-08-1987

NONE

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07K 14/485, A61K 38/18</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/54356</b> <b>(43) International Publication Date:</b> 28 October 1999 (28.10.99)
<b>(21) International Application Number:</b> PCT/GB99/01211 <b>(22) International Filing Date:</b> 21 April 1999 (21.04.99) <b>(30) Priority Data:</b> 9808407.2      22 April 1998 (22.04.98)      GB <b>(71) Applicant (for all designated States except US):</b> THE QUEEN'S UNIVERSITY OF BELFAST [GB/GB]; 8 Malone Road, Belfast BT9 5BN (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> NELSON, John [GB/GB]; 59 Ashley Avenue, Belfast BT9 7BU (GB). WALKER, Brian [GB/GB]; 10 Castleview, DUNDRUM BT33 0AS (GB). McFERRAN, Neil [GB/GB]; 65 Marlborough Park South, Belfast BT9 6HS (GB). HARRIOTT, Patrick [GB/GB]; 12 William Alex Park, Finaghy, Belfast BT10 0LN (GB). <b>(74) Agent:</b> MURGITROYD & COMPANY; 373 Scotland Street, Glasgow G5 8QA (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PEPTIDE FRAGMENTS OF MURINE EPIDERMAL GROWTH FACTOR AS LAMININ RECEPTOR TARGETS <b>(57) Abstract</b> <p>The present invention provides the use of natural, synthetic or modified peptide factors derived from murine epidermal growth factor in the treatment of angiogenic diseases by targeting laminin receptors. The invention provides agonists and antagonists which may be modified to prevent proteolytic degradation. Use of the invention to treat retinopathy of prematurity and promote wound healing is envisaged.</p>		

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01211

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07K14/485 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	MCFERRAN, NEIL V. ET AL: "A peptide molecular dynamics study correlates structure with function" BIOCHEM. SOC. TRANS. (1996), 24(1), 127S , 1996, XP002116636 page 127S, left-hand column, paragraph 4	1-4,7-10
	-/-	



Further documents are listed in the continuation of box C.



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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

27 September 1999

Date of mailing of the international search report

12/10/1999

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Fuhr, C



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01211

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4686283 A	11-08-1987	NONE	